REMARKS

Claims 245, 248-251, 253-255, 260, 264, 268, 270, 270, 272, 284, 288-290. 296, 299, 303 304, 308-313 and 318-325 are pending in the above-referenced application. Claims 318-324 have been withdrawn. As will be discussed in further detail below, claims 245, 265, 299 and 325 have been amended to more distinctly claim that which Applicants regard as the invention. New claim 326 has been added to recite a specific embodiment, particularly, a multi-cassette nucleic acid construct comprising at least three promoters, which upon introduction into a eukaryotic cell produces at least one specific nucleic acid from each of said promoters, where each specific nucleic acid produced is substantially nonhomologous with each other and is complementary with a specific portion of one or more HIV RNAs in a cell or binds to a specific HIV protein and being either. As will also be discussed in further detail below, the amended claims and new claim 326 are supported by the specification.

I. SUBSTANCE OF INTERVIEW

Applicants wish to thank Examiner Hudson for her time and helpful suggestions during their telephonic interview with the undersigned, the Examiner's representative, Cheryl H. Agris and one of the inventors, Dr. James Donegan on October 7, 2008. The substance of the interview is discussed below.

A. Brief Description of any Exhibit Shown or any Demonstration Conducted

Applicants submitted pages 91-93, 103-104, 106-107, 159-167 and Figures 37-43 and 46 of the specification since these pages and figures were referred to during the interview.

B. Identification of Claims Discussed

Claims 245, 265, 299 and 325 were discussed.

C. Identification of Specific Prior Art Discussed

As will be set forth in further detail below, Calabretta et al. and Deitz et al. were discussed with respect to the rejections under 35 USC §103.

D. Identification of Principal Proposed Amendments of a Substantive Nature Discussed

Amendments to claims 245, 265, 299 and 325 were discussed.

E. Identification of General Thrust of Principal Arguments presented to the examiner

An adequate description has been provided to support the pending claims. No new matter is contained in the pending claims. Further, claims 299, 303, 304, 308-313, 324 and 325 are not obvious over the cited references. Dietz et al. would not be pertinent prior art since the filing date of Dietz et al. is after the priority date of the instant application.

F. A General Indication of Any other Pertinent Matters Discussed

Applicants discussed the possibility of adding a new claim to specifically recite that the multi-cassette construct that expresses sequences complementary to HIV RNAs or that bind to specific HIV proteins.

G. General Results or Outcome of the Interview

Applicants agreed to submit arguments to support assertions of adequate written description and further agreed to point out with specificity sections of the specification that support the instant claims. Furthermore, Applicants will set forth arguments as to why claims 299, 303, 304, 308-313, and 324 and 325 are not obvious over the cited references. Applicants will also present a new claim directed to a multi-cassette construct directed to the expression of specific nucleic acid being either complementary with a specific portion of one or more HIV RNAs in a cell or binding to a specific HIV protein.

II. The Rejection Under 35 USC 112, First Paragraph

A. Rejection of Claims 265, 268, 270, 272, 284, 288-290, and 296

Claims 265, 268, 270, 272, 284, 288-290, and 296, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement; these claims are asserted to recite new matter. The Office Action specifically states:

> Claim 265 recites, "said antisense nucleic acid sequence replacing sequences that participated in stem-loop formation in said snRNA". Although Figure 41 depicts a U1 with antisense sequence inserted, there is not support for molecules having each of the characteristics of claim 265 and an antisense nucleic acid sequence that replaces sequences that participated in stem-loop formation in any snRNA, as instantly recited. Claims 268, 270, 272,284, 288-290, and 296 are rejected because they depend from claim 265.
>
> Applicant argues that Figure 41 displays an antisense sequence replacing sequences that participate in stem-loop formation. The example in Figure 41 does not offer support for the specific terminology or breadth that is recited in instant claim 265. Applicant also points to text in the specification for support for the claim language. Applicant points to Example 26 on page 182 for an example of BclI and Bsp E1 being used to remove a 49 base segment of the U1. This specific example pointed to by applicant does not offer support for the broad language of the instant claims, which is not directed to the specifics of the example. The specification does not disclose support commensurate in breadth with the instant claim language.
>
> There is no support for this claim limitation in the claimed priority documents.
>
> Therefore, the effective filing date of claims 265, 268, 270, 272, 284, 288-290, and 296 is considered, for purposes of prior art, to be 11/25/97, which is the filing date of the instant application.

Applicants respectfully traverse the rejection. It is Applicants assertion that there is indeed support in both the Application and the figures for claim 265. Below is a table summarizing the support for claim 265:

Claim Language	Support
An isolated nucleic acid construct which when present in a cell acts as a template for the synthesis of a nucleic acid comprising (i) a nuclear localization sequence comprising a portion of snRNA, said portion of snRNA comprising sequences for	p. 103, lines 11-15
(a) at least two stem loops present at the 3' end of native snRNA, and	Pg. 104, lines 4-8; sentence bridging pp. 163-164; Figure 41, 2nd and 3rd diagrams (C and D loops) and Figure 43
(b) a reimportation signal and	Sm region depicted in Figure 41 and p. 15, lines 4-7 (Sm is reimportation signal)
(ii) an antisense nucleic acid sequence, said antisense nucleic acid sequence replacing sequences that participated in stem-loop formation in the native form of said snRNA.	Pg. 103, line 11 to page 104, line 3. Figures 41 and 43 depicts replacing stem-loop sequences with antisense sequences.

Applicants also herewith submit as Exhibit 1 annotated Figures 41 and 43. With regards to the process seen in figure 41, a normal U1 is shown with what are termed Stem/Loop I, Stem/Loop II, Stem/Loop III and Stem/Loop IV. In the second step of the process, U1 sequences have been removed (excised). It can be specifically seen here that the sequences for the loop and A' segment involved in formation of Stem/Loop I and the sequences for the loop and B segment involved in the formation of Stem/Loop II in the native U1 molecules have been eliminated. Applicants have also amended claim 265 to recite that the antisense nucleic acid sequence replaces sequences that participated in stem-loop formation **in the native form** of the snRNA. In the third step, "Anti-sense sequences" are inserted into the molecule. Figure 41 also shows that the two stem/loops at the 3' end (Stem/Loop III and Stem/Loop IV) are preserved and the "Sm region" that is involved in

reimportation of snRNA's into the nucleus remains intact in the construct. A description of the process and constructs shown in Figures 41 and 43 is provided in the specification (Example 26, pp. 102-104, specifically p. 103, line 11 to p. 104, line 8). Further, as noted above, the "Sm region" is stated in the specification on page 15 to be involved in reimportation: "The binding of spliceosome proteins present in the cytoplasm to **the Sm region** of the U1 RNA in combination with hypermethylation is believed to generate a signal for the **reimportation of the RNA back into the nucleus**". It was further stated in Example 26: "As described earlier, the design of he cloning method should allow the insertion of novel sequences that will still allow the utilization of signals provided by the U1 transcript for nuclear localization…."[see p. 163, lines 14-17). Further in this passage it was stated "In FIG. 43 it can be seen that despite changes in the 5' end (where the new sequences have been introduced) loops III and IV as well as the Sm region remain undisturbed" (sentence bridging pp. 163-164).

Claims 268, 270, 272, 284, 288-290 and 296 depend from claim 265. Therefore, arguments made with respect to claim 265 would apply to these claims as well.

Further, Applicants note that the priority document dated December 15, 1995 is identical to the instant application. Thus, the effective filing date of these claims are indeed December 15, 1995 not November 25, 1997.

In view of the above arguments and the amendment of claim 265, Applicants assert that the rejections of claims 265, 268, 270, 272, 284, 288-290 and 296 under 35 USC 112, first paragraph (new matter) have been overcome. Therefore, Applicants respectfully request that the rejection be withdrawn.

B. Claims 245-255, 260, 264, 299, 303, 304, 308-313, 324 and 325

The Office Action specifically asserts

> Claim 245 recites that the secondary nucleic acid or gene product "does not act as a template for the synthesis of said primary nucleic acid". However, the instant specification does not disclose this limitation.
>
> Claim 299 recites that the isolated multi-cassette nucleic acid construct comprises "at least three promoters and/or

at least three initiators". However, the instant specification does not disclose this limitation.

Claims 246-255, 260, 264, 303, 304, 308-313 and 324 are rejected because they depend from claim 245 or claim 299.

Newly added claim 325 is not fully supported by the specification. The specification does not teach isolated multi-cassette nucleic acid constructs comprising either more than one promoter or more than one initiator or both, wherein said promoter is a snRNA promoter or bacteriophage promoter which upon introduction into a eukaryotic cell produces more than one specific nucleic acid, each such specific nucleic acid being substantially nonhomologous to each other and being either complementary with a specific portion of one or more viral or cellular RNAs in a cell or binds to a specific viral or cellular protein, wherein each specific nucleic acid binds to different target nucleic acid sequences. The specification does not teach the combination of each of these specific elements.

There is no support for this claim limitation in the claimed priority documents. Therefore, the effective filing date of claims 245-255, 260, 264, 299, 303, 304, 308-313, 324 and 325 is considered, for purposes of prior art, to be 11/25/97, which is the filing date of the instant application.

Applicants respectfully traverse the rejection. It is Applicants assertion that there is indeed support in both the application and the figures for claims 245, 299 and 325. Below is a table summarizing the support for each of these claims:

Claim	Recitation	Support
245	A composition comprising (a) an isolated primary nucleic acid construct comprising a primary nucleic acid, which upon introduction into a eukaryotic cell acts as a template for the synthesis of a secondary nucleic acid which acts as a template for the synthesis of a gene product, selected from the group consisting of a sense and antisense nucleic acid in said eukaryotic cell, wherein said secondary nucleic acid or said gene product **does not act as a template for the synthesis of said primary nucleic acid** and	p.92, par. 1, p. 93, par. 3, Examples 23-25, diagrammatically depicted in Figs. 37-39
	(b) a signal processing sequence.	Page 96, lines 12-15: "When the above-described compositions further comprise a signal processing sequence, such sequences can be selected from a promoter, an initiator…."
299	An isolated multi-cassette nucleic acid construct comprising at least three promoters, which upon introduction into a eukaryotic cell produces at least one specific nucleic acid from each of said promoters, each such specific nucleic acid so produced being substantially nonhomologous with each other and being either complementary with a specific portion of one or more viral or cellular RNAs in a cell or binds to a specific viral or cellular protein, wherein each specific nucleic acid binds to different target nucleic acid sequences.	Example 27 ("Construction of a Multi-Cassette Construct which expresses three antisense sequences as part of U1 snRNA"), pp. 164 and depicted in Figure 46; Example 28 ("Construction of an Antisense Expressing Multi-cassette Construct Containing Three T7 RNA Promoters", pp. 165-166 and Figure 46; Example 29 ("Construction of an Antisense Expressing Multi-Cassette Construct Containing Three T7 RNA Promoters and Intron-Containing T7 RNA Polymerase Gene"), pp. 166-167, depicted in Figure 47.

325	An isolated multi-cassette nucleic acid construct **comprising more than one promoter**, wherein said promoter is **a snRNA promoter or bacteriophage promoter**, which upon introduction into a eukaryotic cell produces more than one specific nucleic acid, each such specific nucleic acid so produced being substantially nonhomologous with each other and being either complementary with a specific portion of one or more viral or cellular RNAs in a cell or binds to a specific viral or cellular protein, wherein each specific nucleic acid binds to different target nucleic acid sequences.	p. 106, lines 1-6 and lines 16-18; an example of snRNA s provided in Example 27 (depicted diagrammatically in Figure 46 and examples of bacteriophage promoters are provided in Examples 28 and 29 and depicted in Figure 47).

Applicants respectfully point out with respect to claim 245 that it is stated on page 92, paragraph 1, it is stated:

> The generation or formation of a Production Center from a Primary Nucleic Acid Construct or the generation or formation of a Production Center from another Production Center. However, production centers cannot produce a Primary Nucleic Acid Construct.

A production center is defined on page 91, lines 14-19 as follows:

> As used herein, the term production center is intended to cover secondary nucleic acid components which can be produced from a primary nucleic acid construct. Also covered are a tertiary nucleic acid which could be produced from the secondary nucleic acid component, as well as any nucleic acid product which may be produced from the secondary nucleic acid component.

Furthermore, it is stated on page 93, lines 11-17:

> Thus, a significant embodiment of this invention concerns a composition comprising a primary nucleic acid component which upon introduction into a cell produces a secondary nucleic acid component which is capable of

> producing a nucleic acid product, or a tertiary nucleic acid component, or both. The secondary and tertiary nucleic components and the nucleic acid product are incapable of producing the primary nucleic acid component.

The term "nucleic acid component" is defined in the paragraph bridging pages 93 and 94 as:

> In the present composition, the primary nucleic acid component can comprise a nucleic acid, a nucleic acid construct, a nucleic acid conjugate, a virus, a viral fragment, a viral vector, a viroid, a phage, a phage vector, a plasmid, a plasmid vector, a bacterium and a bacterial fragment or combinations of any of these.

Thus, the term "nucleic acid component" encompasses a nucleic acid construct or nucleic acid.

Specific examples of production centers are provided in Figures 37-40. Annotated copies of these Figures are attached hereto as Exhibit 2. A description of Figures 37-39 is provided in Examples 23 (describes Figures 37 and 38), 24 (describes Figure 39) and 25 (describes Figure 40).

Claims 299 and 325 are directed to multi-cassette constructs. Applicants further note that claims 299 and 325 have been amended to recite that the constructs comprise "promoters". There is no mention regarding initiators. A general description is provided on page 106. In particular, p. 106, lines 1-6, states:

> This invention provides a nucleic acid component which upon introduction into a cell is capable of producing more than one specific nucleic acid sequence. Each such specific sequence so produced are substantially nonhomologous with each other and are either complementary with a specific portion of a single-stranded nucleic acid of interest in a cell or are capable of binding to a specific protein of interest in a cell.

A nucleic acid component is described on page 106, lines 10-13 as follows:

> The present nucleic acid component can be derived or selected from any of nucleic acids, nucleic acid constructs, nucleic acid conjugates, a virus or fragment, a phage, a plasmid, a bacterium, or fragment, a vector.."

It is further noted in the paragraph bridging pages 106 and 107 that the nucleic acid component "can comprise either more than one promoter.."

Specific examples of multi-cassettes are described in Examples 28-29 and depicted in Figures 46-47. Annotated copies of these Figures are attached hereto as Exhibit 3.

Claims 246-255, 260 and 264 depend from claim 245 and claims 303, 304, 308-313 and 324 depend from claim 299. Therefore, arguments made with respect to claims 245 and 299 would apply to these claims as well.

Further, Applicants note that the priority document dated December 15, 1995 is identical to the instant application. Thus, the effective filing date of these claims are indeed December 15, 1995 not November 25, 1997.

In view of the above arguments and the amendments of claims 245, 299 and 325, Applicants assert that the rejections of claims 245-255, 260, 264, 299, 303, 304, 308-313, 324 and 325 under 35 USC 112, first paragraph (new matter) have been overcome. Therefore, Applicants respectfully request that the rejection be withdrawn.

III. The Rejections Under 35 USC 103

Two rejections were made under 35 USC 103. These are described below.

A. The Rejections of Claims 299, 303, 304, 308-313, and 324

Claims 299, 303, 304, 308-313, and 324 are rejected under 35 U.S.C. 103(a) as being unpatentable over Calabretta et al. (US 5,734,039), in view of Binkley et al. (Nucleic Acids Research, 1995, Vol. 23, No. 16, pages 3198-3205), and Craig et al. (WO 95/08635). The Office Action specifically states:

> ....It would have been obvious to incorporate sequences for the production of three or more different antisense sequences rather than the two different antisense sequences of Calabretta et al. It would have been obvious to incorporate RNA oligonucleotides that bind to proteins, as taught by Binkley et al. in place of the antisense oligonucleotides taught in the system of Calabretta et al. It would have been obvious to use the

SELEX method to assay for RNA molecules that bind to a protein, as taught by Binkley et al. and to specifically use a decoy protein as the protein, as taught by Craig et al. One would have been motivated to incorporate at least three promoters to produce at least three antisense sequences instead of the two promoters to produce two different antisense sequences as taught by Calabretta et al. to optimize the activity of the multi-cassette nucleic acid construct of Calabretta et al. Since Calabretta et al. teaches utilizing a multi-cassette nucleic acid construct to deliver sequences that are transcribed into two different active antisense nucleic acid molecules that act synergistically in the cell, one would have certainly been motivated to incorporate three or more promoters for the production of three or more antisense sequences as well, for the same exact reasons as utilizing two.

One would have been motivated to incorporate RNA oligonucleotides that bind to proteins instead of the antisense oligonucleotides in the system of Calabretta et al. because Binkley et al. teach that high affinity RNA ligands to proteins, such as NGF that localizes NGF-sensitive growing axons, can be easily isolated using the SELEX procedure and teach that such RNAs may furnish useful diagnostic tools for the study of proteins. Since both types of nucleic acid oligonucleotides are used to determine binding interactions, as evidenced by the teachings of Calabretta et al. and Binkley et al., one would have been motivated to express the RNA ligands taught by Binkley et al. in the system of Calabretta et al.

One would have been motivated to screen for resultant RNA aptamers against a decoy protein because Binkley et al. teach that high affinity RNA ligands to proteins can be easily isolated using the SELEX procedure and teach that such RNAs may furnish useful diagnostic tools for the study of proteins. Since Craig et al. teach that decoy proteins are proteins that are useful to serve as a mutant that is capable of binding to a preferred site but yet is incapable of activating transcription, one would have been motivated to use the SELEX method of Binkley et al. to identify RNA ligands to any known protein, such as the decoy proteins of Craig et al.

One would have a reasonable expectation of success given that each of the nucleic acid molecules were known to bind with target molecules in a sequence specific manner, as evidenced by Calabretta et al. and Binkley et

> al. One would have a reasonable expectation of success to express the protein binding RNA molecules of Binkley et al. in the dual system of Calabretta et ai., with the advantage of producing two different binding molecules at once.
>
> One would have a reasonable expectation of success given that Craig et al. teach the benefits of decoy proteins and Binkley et al. teach assaying for RNA aptamers to proteins and teach a method (SELEX) that is widely use to identify RNA molecules that bind to known proteins.

Applicants respectfully traverse the rejection. With regard to comments on the Calabretta et al., it is important to note the motivation for the use of more than one antisense. In Applicants view, it would not be obvious to combine Calabretta et al. with Binkley et al. and Craig et al. to obtain the construct of the present invention. The Office Action characterizes Calabretta et al. as follows:

> According to another embodiment, the invention is an artificially-constructed gene comprising a first promoter segment and a segment containing a cytoplasmic oncogene and a second promoter and a segment containing DNA of a nuclear oncogene or proto-oncogene. The oncogene/-proto-oncogene DNA-containing segments are in inverted orientation such that transcription of the artificially-constructed gene produces RNA comlementary to an mRNA transcript of the cytoplasmic oncogene and RNA complementary to an mRNA transcript of the nuclear oncogene or proto-oncogene.

Applicants further note that Calabretta et al. further states "Oncogene/proto-oncogenes are broadly subdivided into two major groups: nuclear and cytoplasmic." (Column 2 lines 44-45). The entire principle that is being described in Calabretta et al. is connected to the existence of two (and only two) different compartments where the protein products of oncogenes might act: the nucleus or the cytoplasm. Once nuclear and cytoplasmic compartments have been addressed, there is no third locale that would be separate from nucleus and cytoplasm and requires a separate targeting strategy. It should be noted that in the context of discussing genetic antisense expressed from a construct the above citation only makes references to a first and second promoter and has no mention of "one or more" language. If there

are more than one target sequences that are nuclear, the specification remains silent of whether multivalent or separate transcripts would be of use and correspondingly the same silence with regard to cytoplasmic targets. The logical progression from Calabretta in terms of the art at the time Calabretta was published would be that a desire for more than one anti-sense target would be carried out by a combination of nuclear antisense sequences into a multivalent cytoplasmic target transcript from one promoter and a multivalent nuclear target transcript from a second promoter. The purpose of a second promoter in Calabretta is not to increase the number of transcripts per se but to add additional properties such that if the first promoter is for nuclear specific antisense genes then a second promoter can be used specifically for cytoplasmic genes and as such no motivation exists for the presence of a third promoter. The transcriptional embodiment is described in more detail in a section spanning (column 19, line 40 to column 20, line 9) discussing possible constructs. Again, there seems to be no suggestion or description of any utility of having more than the two cited (cytoplasmic and nuclear) operons.

Applicants further wish to emphasize that there are two separate problems being addressed in the present invention and the Calabretta et al. The latter described two different promoters due to concerns with two different classes of oncogenes: nuclear and cytoplasmic. The utility for three or more separate transcription products in the present invention was addressing the problem of mutability and variance where the pool of target molecules in pathogens such as HIV encompass a variety of sequences that may escape inactivation by only one or two antisense sequences. For instance, witness the current use of a triple drug therapy for treatment of HIV for exactly the same reasons of avoidance of the unlikely occurrence of pre-existing immunity to each of the drugs at the start of the drug regimen, whereas single drug therapies rapidly induce the presence of a resistant population. As discussed in the response to the previous Office Action, this mutability is a product of the viral mode of propagation and does not translate into the oncogene targets described by Calabretta et al. which should have much, much lower mutation frequencies. Clearly, there was no suggestion regarding introducing

three or more sequences. It would not occur to one of skill in the art to try to even obtain such a construct.

The other cited references would be of limited significance. Binkley et al. merely teaches molecules that may bind to cellular protein. Craig et al. merely teaches expression of a viral decoy protein. In Applicants view, it would not be obvious to combine all of these references. As noted above, combining Binkley et al. with Calabretta et al. would at best provide a construct that expresses two specific RNA sequences that binds to a cellular protein. Further, there was no suggestion regarding combining Craig et al. with the other two. Craig et al. merely teaches the cloning of a protein and its therapeutic uses. There is no teaching regarding binding to a specific nucleic acid or facilitate transport.

Claims 303, 304, 308-313, and 324 depend from claim 299. Therefore, arguments made with respect to claim 299 would apply to these claims as well.

In view of the above arguments, Applicants assert that the rejections of claims 299, 303, 304, 308-313 and 324 have been overcome. Therefore, Applicants respectfully request that the rejections be withdrawn.

B. The Rejection of Claims 299, 303, 304, 308-313, 324 and 325

Claims 299, 303, 304, 308-313, 324 and 325 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Calabretta et al. (US 5,734,039), in view of Binkley et al. (Nucleic Acids Research, 1995, Vol. 23, No. 16, pages 3198-3205), and Craig et al. (WO 95/08635) as explained in the rejection under 35 U.S.C. 103(a) above, further in view of Dietz (US 5,814,500). The Office Action specifically states:

> The invention of the above claims is directed to an isolated multi-cassette nucleic acid construct comprising at least three promoters and/or initiators, which upon introduction into a eukaryotic cell produces at least one specific nucleic acid from each of said promoters or initiators, each such specific nucleic acid so produced being substantially nonhomologous with each other and being either complementary with a specific portion of one or more viral or cellular RNAs in a cell or binds to a specific viral or cellular protein, wherein each specific nucleic acid binds to different target nucleic acid sequences. The specific nucleic acid binds to a specific cellular protein comprising a localizing protein or a decoy

> protein. The specific nucleic acid binds to a specific cellular protein comprising a localizing protein or a decoy protein. The multi-cassette nucleic acid comprises a snRNA promoter.
>
> Calabretta et al. does not teach constructs having a snRNA promoter.
>
> Dietz teaches nucleic acid constructs for the delivery of antisense targeting sequences and teaches that preferably a snRNA promoter is included in the construct. Dietz teaches that the construct comprises stem loop structures that flank the antisense nucleic acid so that the antisense oligonucleotide can readily interact with any target sequence. Dietz teaches that the stem loops are preferably U1 snRNA stem loops and there is a cloning site into which virtually any antisense oligonucleotide could be inserted. Dietz teaches that the construct may be used to introduce sequences to create transgenic animals. Dietz teaches delivery of the construct to a cell and teaches a cell comprising the construct, as well as a biological system comprising the cell. For example, Dietz teaches that the constructs may be introduced into mice, rodents (e.g. rat, hamster), rabbits, chickens, sheep, goats, fish, pigs, cattle, and non-human primates. Administration of the construct of the invention can be *in vivo, in vitro* or *ex vivo*.
>
> It would have been obvious to incorporate the snRNA promoter of Dietz into the constructs of Calabretta et al....

Applicants respectfully traverse the rejection. As stated in the Office Action, Calabretta et al. does not teach snRNA promoters. Further, Calabretta et al. does not teach bacteriophage promoters. Applicants also wish to point out that Binkley et al. and Craig et al. do not disclose snRNA or bacteriophage promoters. Dietz in Applicants' view should not be applied as prior art. This is because the filing date of the Dietz patent, October 31, 1996 is about 10 months after the priority date of the instant application, December 15, 1995. As discussed above, Applicants assert that they are entitled to the priority date. Even assuming *arguendo* that Dietz could be applied as prior art, Applicants assert that Dietz seemed to teaching ways that would result in constructs that remain in the cytoplasm rather than the nucleus and teaching away from nuclear targeting of anti-sense.

Claims 303, 304, 308-313, and 324 depend from claim 299. Therefore, arguments made with respect to claim 299 would apply to these claims as well.

In view of the above arguments, Applicants assert that the rejections of claims 299, 303, 304, 308-313, 324 and 325 have been overcome. Therefore, Applicants respectfully request that the rejections be withdrawn.

IV. New Claim 326

Applicants note that new claim 326 has been added. It is directed to a multi-cassette construct comprising at least three promoters, which upon introduction into a eukaryotic cell produces at least one specific nucleic acid from each of said promoters, where each nucleic acid is either complementary with a specific portion of one or more HIV RNAs in a cell or binds to **a specific HIV protein**. New claim 326 is supported by the specification in Example 27 (depicted diagrammatically in Figure 46). Specifically Example 27 and Figure 46 depicts the expression of HIV sequences ("A Antisense" of "Anti-A", "B Antisense" of "Anti-B", "C Antisense" or "Anti-C". Applicants note that Example 27 refers to Example 19. Example 19, (particularly the paragraph bridging pp. 152-153 entitled "E) Antisense sequences" describes the sources of these sequences. Applicants further assert that new claim 26 is not anticipated or obvious over the cited references. Specifically, there was no suggestion of expression of HIV sequences from multi-cassette constructs.

SUMMARY AND CONCLUSIONS

It is Applicants belief that the pending claims are in condition for allowance. However, if a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney request that he be contacted at the number provided below.

Respectfully submitted,

/Cheryl H Agris/

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